REMARKS

Status of the Claims

Claims 1-14, 18-21 and 24-29 are currently pending in the application. Claims 1-4, 18-24 and 27 stand rejected. The Examiner objects to claims 5-14, 25, 26 and 28. Claims 1, 5-10, 12-14, 18-19, 21, and 24-28 have been amended as set forth herein. Claims 15-17, 22 and 23 have been cancelled herein. All amendments and cancellations are made without prejudice or disclaimer. New claim 29 has been added herein. No new matter has been added by way of the present amendments. Specifically, the amendment to claim 1 is supported by the specification at page 4, lines 1-15 and at page 4, Summary of the Invention, first paragraph. Amendment to claim 21 is supported by the specification at page 7, first and sixth paragraph, and Example 3, page 22. The remaining changes to the claims are only clarifying amendments to conform the claims more closely to U.S. practice and amendments to change dependency and do not narrow the scope of the claims. New claim 29 is supported by original claim 1. Reconsideration is respectfully requested.

Information Disclosure Statement

Applicants note that the Examiner returned a copy of the PTO/SB/08 form having crossed out the citations and thus the Examiner has not considered the references submitted with the Information Disclosure Statement filed on April 28, 2004. Applicants understand that the PCT receiving office, or the IB, typically forwards these references to the USPTO. However, if the Examiner experiences difficulty in obtaining copies of the references, the Examiner is

respectfully requested to contact Applicants' representative at the number provided at the end of this paper for assistance in procuring copies of the references.

Objections to the Claims

The Examiner objects to claims 5-14, 25, 26 and 28 under 37 C.F.R. § 1.75(c) as being in improper form. (*See*, Office Action of April 20, 2006, at page 2, hereinafter, "Office Action"). Specifically, the Examiner states that multiple dependent claims should refer to other claims in the alternative only, and/or, cannot depend from any other multiple dependent claim. (*Id.*). Claims 5, 8-10, 12-14, 25, 26 and 28 have been amended to correct dependency as shown in the claims listing, above.

Additional amendments have been made to the form of the claims to better conform their language to U.S. practice.

Reconsideration and withdrawal of the objection to claims 5-14, 25, 26 and 28 are respectfully requested.

Rejections Under 35 U.S.C. § 102(b)

Larner, U.S. Patent No. 5,750,348

Claim 1 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Larner, U.S. Patent No. 5,750,348 (hereinafter referred to as "Larner"). (*See*, *Id.*, at page 3). Applicants traverse the rejection as set forth herein.

The Examiner states that Larner discloses a method for detecting mild impaired glucose tolerance by quantitatively determining myo-inositol levels in urine samples and evaluating cases where the level shows a characteristic value higher than control as impaired glucose tolerance or an insulin secretory defect. (*Id.* citing column 2, lines 5-60 of Larson).

As a preliminary matter, the Examiner's attention is directed to the fact that "insulin resistance," "mild impaired glucose tolerance" and "insulin secretory defect," are different terms relating to different biochemical problems. For instance, "mild impaired glucose tolerance," as recited in present claim 1, is classified as NGT (normal glucose tolerance), but refers to a slight decrease in glucose tolerance, as disclosed in detail at page 4, lines 4-11 of the present specification. This is a new classification.

Claim 1 recites, "A method of detecting mild impaired glucose tolerance in a subject, wherein the method comprises: providing a sample from a subject; quantitatively determining the myo-inositol level in a sample; and determining that the subject has mild impaired glucose tolerance or that the subject has an insulin secretory defect based on the concentration of myo-inositol in the sample, wherein a concentration of myo-inositol at a characteristic value or higher than a characteristic value indicates the subject has mild impaired glucose tolerance or the subject has an insulin secretory defect."

In contrast, Larner discloses a method for detecting "insulin resistance or type II diabetes," and not a method for detecting "mild impaired glucose tolerance." Type II diabetes or insulin resistance relates to defects in utilization of glucose by tissues. Thus, Larner does not disclose mild impaired glucose tolerance or insulin secretory defects, as recited in the present claims. Larner discloses a method of screening for insulin resistance or type II diabetes wherein

a "myo/chiro ratio" exceeds a value that is characteristic of insulin resistance, said "myo/chiro ratio" being obtained by measuring levels of myoinositol and D-chiroinositol. Larner does not disclose the step of determining that the subject has mild impaired glucose tolerance or that the subject has an insulin secretory defect based on the concentration of myo-inositol in the sample, wherein a concentration of myo-inositol at a characteristic value or higher than a characteristic value indicates the subject has mild impaired glucose tolerance or the subject has an insulin secretory defect, as presently recited in claim 1.

Furthermore, the Examiner's attention is directed to the "First Degree Relative of Type 2 Diabetes" column in Table 1 of Larner at column 2, lines 30-42. The myoinositol level disclosed in Table 1 of Larner is the same as that of a normal population. Even if the myoinositol level is the same, insulin resistance or type II diabetes can be detected by "myo/chiro ratio" according to Larner's disclosure.

Claim 1 is directed to a method of detecting "mild impaired glucose tolerance" and "insulin secretory defect" by evaluating a case wherein a myo-inositol level is higher than a characteristic value. Specifically, claim 1 recites, in part, "wherein a concentration of myo-inositol at a characteristic value or higher than a characteristic value indicates the subject has mild impaired glucose tolerance or the subject has an insulin secretory defect." Thus, claim 1 is directed to those instances where the myo-inositol level is higher than that of a normal population, whereas the method according to Larner is directed at instances where the myo-inositol level is the same as a normal population. This difference in populations is defined as the difference between "insulin resistance or type II diabetes," and "mild impaired glucose tolerance," as mentioned above, and in the specification at pages 2-4.

As explained above, the Examiner should further consider that insulin resistance and type II diabetes arise from defects in metabolism in peripheral tissues; they become unable to respond to insulin. Such would be in contrast to a defect in secretion of insulin.

Thus, since "insulin resistance" and "Type II diabetes" are not the same as an "insulin secretory defect", and "mild impaired glucose tolerance", Larner does not anticipate the presently claimed invention because Larner is directed to a different method. That is, the method of Larner is directed to detecting a different population of individuals as compared to the presently claimed method. Since Larner's method is different, Larner does not disclose each and every limitation of the presently claimed method and therefore the disclosure of Larner does not anticipate claim 1 of the present invention.

Reconsideration and withdrawal of the anticipation rejection of claim 1 are respectfully requested.

Ashizawa et al., *Journal of Biophysical Methods,* Vol. 44, pp. 89-94 (2000)

Claims 1-4 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Ashizawa et al., *Journal of Biophysical Methods,* Vol. 44, pp. 89-94 (2000) (hereinafter referred to as "Ashizawa et al."). (*Id.*). Applicants traverse the rejection as set forth herein.

The Examiner states that Ashizawa et al. disclose a method for quantitatively determining myo-inositol in a tissue sample using the enzyme myo-inositol dehydrogenase and NADH in an enzymatic cycling method and evaluating cases wherein the level shows a characteristic value in diabetic subjects (insulin secretion defective). (*Id.*, citing Ashizawa et al. at page 90, lines 1-11 and Table 1 at page 93).

Claim 1 recites, "A method of detecting mild impaired glucose tolerance in a subject, wherein the method comprises: providing a sample from a subject; quantitatively determining the myo-inositol level in a sample; and determining that the subject has mild impaired glucose tolerance or that the subject has an insulin secretory defect based on the concentration of myo-inositol in the sample, wherein a concentration of myo-inositol at a characteristic value or higher than a characteristic value indicates the subject has mild impaired glucose tolerance or the subject has an insulin secretory defect."

Ashizawa et al. do not disclose a method for determining mild impaired glucose tolerance, as recited in claim 1. In fact Ashizawa et al. only disclose methods of assaying myo-inositol in a sample. Thus, the disclosure of Ashizawa et al. is entirely devoid of any direction on how to determine if a subject is suffering from mild impaired glucose tolerance.

Further, Ashizawa et al. disclose the preparation of diabetic rats as a model to evaluate the effect of a new ARI (aldose reductase inhibitor), GP-1447, and disclose measuring a myo-inositol level in the sciatic nerve and lens in the ARI-administered group and the ARI-non-administered group. The myo-inositol level of normal rats is higher than that of diabetic rats in Ashizawa et al. while the myo-inositol level of a normal model is lower in the present invention. (*See*, Ashizawa et al. at Table 1). This fact indicates that the method of measurement is different in Ashizawa et al. compared to the presently claimed invention.

Since Ashizawa et al. do not disclose each and every limitation of the presently claimed invention, according to claim 1, especially the second step of claim 1, Ashizawa et al. cannot anticipate the presently claimed invention.

Dependent claims 2-4 are not anticipated, *inter alia*, as depending from a non-anticipated base claim, claim 1.

Reconsideration and withdrawal of the anticipation rejection of claims 1-4 are respectfully requested.

Rejections Under 35 U.S.C. § 103(a)

Ashizawa et al. & Tazoe et al., U.S. Patent No. 6,309,852

Claims 1-4, 18-20 and 27 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Ashizawa et al. in view of Tazoe et al., U.S. Patent No. 6,309,852 (hereinafter, "Tazoe et al."). (*See*, Office Action, at page 4). Applicants traverse the rejection as hereinafter set forth.

The Examiner states that Ashizawa et al. do not disclose a method using two kinds of kinases, wherein the kinases are ATP-hexokinase and an ADP-eliminating agent. (*Id.* at page 5). The Examiner cites to the disclosure of Tazoe et al. for these missing elements and states that Tazoe et al. disclose the use of kinases ADP-dependent hexokinase and 6-phosphofructokinase in combination. (*Id.*). The Examiner states that it would have been obvious to modify the disclosure of Ashizawa et al. to add the kinases disclosed in Tazoe et al. to achieve the dual advantages of removing glucose by two means and removing potentially interfering ADP. (*Id.* at page 6).

However, as stated above, with respect to the anticipation rejections of claims 1-4, Ashizawa et al. do not disclose each and every element of the presently claimed invention. The disclosure of Ashizawa et al. does not mention mild impaired glucose tolerance nor how to determine if a subject may be suffering from this condition. No direction is provided at all in

Ashizawa et al. for determining whether a subject is suffering from mild impaired glucose tolerance.

The disclosure of Tazoe et al., while it may disclose methods of using kinases, does not cure the defect of the disclosure of Ashizawa et al. discussed above.

Furthermore, Applicants maintain that one of ordinary skill in the art would not be motivated to combine the disclosures of Ashizawa et al. and Tazoe et al. and even if one did, they would not obtain the presently claimed invention, as recited by claim 27, for the following reasons.

The Examiner is reminded that teachings of the references must be considered as a whole. The Examiner may not pick and choose among selected parts of the references to select only those parts favorable to the Examiner's position. (*See*, *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804 (Fed. Cir. 1989)).

With this in mind, Applicants note Ashizawa et al. disclose that ATP-hexokinase catalyzes the following reaction:

$$\text{glucose} + \text{ATP} + Mg^{2+} \rightarrow \text{glucose-6-phosphate} + \text{ADP}$$

Thus, in Ashizawa et al., ATP-hexokinase is used to eliminate glucose in the sample by the above reaction, but Ashizawa et al. do not disclose nor suggest further adding a method to eliminate ADP, contrary to what is stated by the Examiner.

Because this reaction is readily reversible, it has been found necessary to further convert one or the other of the glucose phosphorylation products to completely eliminate glucose. Tazoe describes removal of glucose-6-phosphate. In contrast, the present invention removes ADP.

Tazoe et al. disclose an ADP-hexokinase that catalyzes the following reaction:

glucose + ADP + Mg^{2+} → glucose-6-phosphate + AMP

However, the Examiner must consider the disclosure of Tazoe et al. as a whole. Tazoe et al. disclose Enzyme systems 1-3 in order to eliminate glucose when measuring 1,5-anhydroglucitol in the sample, as follows:

Enzyme system 1 (ADP-hexokinase, or ATP-hexokinase, ATP-glucokinase)

glucose + ADP → glucose-6-phosphate + AMP, or

glucose + ATP → glucose-6-phosphate + ADP

Enzyme system 2 (phosphohexose isomerase)

glucose-6-phosphate → fructose-6-phosphate

Enzyme system 3 (6-phosphofructokinase)

fructose-6-phosphate + ATP → fructose-1,6-diphosphate + ADP

(*See*, Tazoe et al., column 4, beginning at line 40). Tazoe et al. disclose that conversion of glucose into glucose-6-phosphate is insufficient in eliminating glucose because the reaction is reversible. (*Id.* at column 4, line 66). The sufficient elimination of glucose was achieved by further converting glucose to fructose-1,6-diphosphate by combining Enzyme systems 2 and 3 with Enzyme system 1. (*Id.* at column 5, lines 2-5). Enzyme System 1 alone was considered by Tazoe et al. to be insufficient for removing glucose from a sample.

Tazoe et al. disclose the use of ADP-hexokinase, phosphohexose isomerase (PHI) and 6-phosphofructokinase (6-PFK) for the purpose of eliminating glucose from the assay by conversion of glucose to fructose-1,6-diphosphate *via* three enzymatic steps. If one of ordinary skill in the art were to combine the teachings of these two references, one would derive a four-

enzyme system including ATP-hexokinase, ADP-hexokinase, PHI and 6-PFK. This hypothetical composition taught by the two cited references is different from the presently claimed invention.

The hexokinase reaction is as follows:

glucose + ATP $\rightarrow$ glucose-6-phosphate (hereinafter, "G-6-P") + ADP

glucose + ADP $\rightarrow$ glucose-6-phosphate + AMP

The compositions of the presently claimed invention are directed at converting ADP. In contrast, the disclosure of Tazoe et al. shows conversion of glucose to G-6-P and G-6-P to fructose-6-phosphate and then fructose-6-phosphate to fructose-1,6-diphosphate, as shown below:

Glucose

↓ ATP-hexokinase, ADP-hexokinase, or ATP-glucokinase

G-6-P + ADP, or AMP

↓ PHI

fructose-6-phosphate

↓ 6-PFK

fructose-1,6-diphosphate

Thus, Tazoe et al. disclose or suggest removal of glucose using hexokinase which results in the unfavorable formation of large quantities of ADP (and, of course, G-6-P). Because Tazoe describes formation of ADP, Tazoe et al. must use ATP-hexokinase to perform this reaction, not ADP-hexokinase. Furthermore, Tazoe et al. do not disclose or suggest the elimination of ADP from the reaction system or that doing so would be useful in eliminating G-6-P (or, ultimately, glucose). In contrast, Tazoe et al. attempts to eliminate G-6-P produced using the first reaction,

above, wherein ADP-hexokinase may be used. Since the first reaction is reversible, G-6-P and ADP interfere with the reaction as these products accumulate and reform glucose and ATP. Thus, Tazoe et al. attempts to remove G-6-P from the reaction system. In contrast, the presently claimed compositions are directed at removing ADP from the system, not G-6-P.

Accordingly, the enzyme system according to the presently claimed invention may be represented as follows:

$$\text{glucose} + \text{ATP} + Mg^{2+} \xrightarrow[\text{ATP-hexokinase}]{} \text{glucose-6-phosphate} + \text{ADP}$$

$$\text{glucose} + \text{ADP} + Mg^{2+} \xrightarrow[\text{ADP-hexokinase}]{} \text{glucose-6-phosphate} + \text{AMP}$$

Thus, according to the presently claimed invention, glucose is converted into glucose-6-phosphate by using two kinds of hexokinase, which results in complete and sufficient elimination of glucose in the present invention. This concept is not in any way disclosed by either reference separately or even when considered in combination.

The present inventors have tried the method of Tazoe et al. for eliminating interference by glucose. As described in the attached Declaration, the method of Tazoe et al. did not work for determination of myo-inositol. Further, Tazoe et al. disclose in Example 6 that glucose concentrations of up to 2 g/dL can be eliminated by their method, whereas Fig. 3 of Reference Example 3 of the present invention discloses that glucose concentrations of up to 10 g/dL can be eliminated by using both ATP-hexokinase and ADP hexokinase of the presently claimed method. Such a result is unexpected by one of skill in the art who considers the disclosures of Tazoe et al. and Ashizawa et al.

Thus, the disclosures of Ashizawa et al. or Tazoe et al., either considered in combination or separately, do not disclose or suggest each and every limitation of the presently claimed invention, especially as recited in claims 1 and 27. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness. (*See*, *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991)). Furthermore, there is evidence of record to rebut any case of *prima facie* obviousness that may be deemed to be properly established.

Since no independent reasoning is provided for the rejection of dependent claims 2-4 and 18-20, these dependent claims are thus also non-obvious, *inter alia*, as depending from a non-obvious base claim, claim 1.

Reconsideration and withdrawal of the obviousness rejection of claims 1-4, 18-20 and 27 are respectfully requested.

Ashizawa et al. & Tazoe et al. & Kozuma et al., U.S. Patent No. 6,046,018

Claims 21-24 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Ashizawa et al. in view of Tazoe et al., and further in view of Kozuma et al., U.S. Patent No. 6,046,018 (hereinafter, "Kozuma et al."). (*See*, Office Action, at page 6). Claims 22 and 23 have been cancelled herein without prejudice or disclaimer, thus obviating the rejection as to claims 22 and 23. Applicants traverse the rejection as to claims 21 and 24 as hereinafter set forth.

The Examiner states that neither Ashizawa et al. nor Tazoe et al. disclose the use of thio-NAD. (*Id.*). The Examiner cites to the disclosure of Kozuma et al. for the missing element. (*Id.*).

However, the combination of the disclosures of Ashizawa et al. and Tazoe et al. and Kozuma et al. do not disclose or suggest the presently claimed compositions according to claims 21 and 24.

As explained above, the combination of Ashizawa et al. with Tazoe et al. does not suggest in any way a combination of myo-inositol dehydrogenase (used to determine the amount of myo-inositol) with ATP-hexokinase and ADP hexokinase. Combining Kozuma et al. with Ashizawa et al. and Tazoe et al. does not remedy the deficiency of the Examiner's alleged *prima facie* case of obviousness.

Furthermore, as explained above and as supported by the attached Declaration of the inventors, the claimed composition provides results not expected by one of ordinary skill in the art. Thus, there is objective evidence of record to rebut any case of unobviousness deemed established by the combination of Ashizawa et al., Tazoe et al. and Kozuma et al.

Since no independent reasoning is provided by the Examiner for the rejection of claim 24, dependent claim 24 is non-obvious, *inter alia*, as depending from a non-obvious base claim, claim 21.

Reconsideration and withdrawal of the obviousness rejection of claims 21-24 are respectfully requested.

CONCLUSION

If the Examiner has any questions or comments, please contact Thomas J. Siepmann, Ph.D., Registration No 57,374 at the offices of Birch, Stewart, Kolasch & Birch, LLP.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

Dated: September 20, 2006

Respectfully submitted,

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